

**PATENT****IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

*In re Application of* )      Group Art Unit: 1633  
Mark J. COOPER *et al.*      )  
Serial No. 10/656,192      )      Examiner: S. Long  
Filed: September 8, 2003      )  
                                )      Confirmation No. 8424  
                                )  
For: Lyophilizable and enhanced compacted nucleic acids

**DECLARATION UNDER RULE 132**

Commissioner of Patents  
Randolph Building  
401 Dulany Street  
Alexandria, VA 22314

Sir:

I, Mark J. Cooper, declare as follows:

1. I am an inventor on the subject application.

2. I am a co-author of Konstan *et al.* "Compacted DNA Nanoparticles Administered

To The Nasal Mucosa Of Cystic Fibrosis Subjects Are Safe And Demonstrate Partial To Complete Cystic Fibrosis Transmembrane Regulator Reconstitution." Human Gene Therapy (2004) 15:1225-1269. The authors are collectively referred to as "Konstan".

3. Konstan made and administered compacted DNA nanoparticle compositions in accordance with the teachings of the subject application. No technology developed after the effective filing date of May 31, 2000 was employed.

4. Specifically, Konstan combined a plasmid containing the human CFTR cDNA with a polyethyleneglycol-modified polycationic peptide to form DNA particles: "The clinical trial material consisted essentially of single molecules of this expression plasmid condensed with a polycationic peptide consisting of an N-terminal cysteine followed by 30 lysine residues (CK<sub>30</sub>) (PolyPeptide Laboratories, Torrance, CA) that was covalently linked to 10-kDa polyethylene glycol (PEG) (Nektar Therapeutics, San Carlos, CA) via a cysteine-maleimide linkage to make CK<sub>30</sub>P10k (Liu *et al.*, 2003)." Page 1258, col.1, lines 21-28. This is the same methodology as taught in Example 2: "These compacted particles consisted of plasmid DNA and PEG-substituted polylysine polymers consisting of 30 lysine residues." Specification at page 17, lines 11-12.

5. Konstan prepared compositions using acetate as a counterion: "The acetate salt of the CK<sub>30</sub>P10k bioconjugate was mixed with plasmid DNA such that complexes were formed having essentially one positive charge for each negative charge on the DNA (Liu *et al.*, 2003)." Page 1258, col. 1, lines 28-30. The subject application taught the use of acetate as a counterion for CK30P10k : "Acetate and bicarbonate bound to CK30P10k and chloride bound to CK45P10k result in slightly positive net charge, while TFA results in electrically neutral complexes." See Example 11 on page 22 of the Specification at lines 18-21.

6. Konstan's compositions are rod-shaped structures: "The DNA was condensed into tightly compacted rod-shaped structures having a diameter of about 12-15 nm and a length of about 100-300 nm." Page 1258, col. 1, lines 31-33. These are the same structures taught in the specification: "DNA condensed with acetate and bicarbonate salts of CK30 polylysine assumed

forms of long (100-300 nm) and narrow (10-20 nm) rods and relaxed toroids (~50-100 nm diameter, 10-20 nm width)...." Specification at page 16, lines 1-3.

7. Konstan delivered the compositions to patients as taught in the subject application. Konstan administered the compositions intranasally: "All subjects received a dose of compacted DNA in saline in one nostril and a dose of vehicle (saline) in the other nostril (each 2 ml) under direct visualization," Page 1257, col. 1, lines 8-10. Example 13 of the specification teaches intranasal delivery of these compositions: "Intranasal gene delivery was assessed for each of the counterion forms of CK30P10K. Twenty five  $\mu$ l of DNA was administered in 5- $\mu$ l aliquots into nostrils of C57/BL6 mice using an automated pipette." Specification at page 23, lines 17-20.

8. Thus, Konstan demonstrates that the methods taught in the application as filed successfully reconstitute CFTR function. Thus, the methods taught in the specification enable the claimed subject matter.

9. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 10/4/07

Mark J. Cooper M.D.

Mark J. Cooper